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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,099	04/15/2004	Hui-Yin Li	PH 7115 DIV2	9263
23914	7590	02/14/2006	EXAMINER	
LOUIS J. WILLE BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			ANDERSON, REBECCA L	
			ART UNIT	PAPER NUMBER
			1626	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/826,099

Applicant(s)

LI ET AL.

Examiner

Rebecca L. Anderson

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-22, 27, 28 and 32 is/are pending in the application.
- 4a) Of the above claim(s) 17-22 and 32-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 17-22, 28 and 32-37 are currently pending in the instant application.

Claims 17-22 and 32-37 are withdrawn from consideration as being for non-elected subject matter. Claim 28 is rejected.

Response to Arguments

Applicant's arguments filed 15 November 2005 have been fully considered but they are not persuasive. Applicant argues that WO 99/32454 discloses compounds which are only ortho substituted on the phenyl ring attached the nitrogen of the pyrazole; that there is no motivation to select all of the necessary variables to arrive at the presently claimed invention and that there is no reason to select the maleic acid salt. These arguments are not persuasive as applicants compounds which are substituted at the meta and para positions are considered positional isomers of the prior art WO 99/32454 and nothing unobvious is seen in substituting the claimed isomer for the structurally similar isomer, as taught by WO 99/32454 since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. In regards to the motivation to select all of the necessary variables to arrive at the presently claimed invention, the prior art provides preferences towards the substituents on applicants' instantly claimed compound as can be seen on pages 13, 18 and 19-21 such as the more preferred embodiment which has an imidazole for A which can be substituted by R4a which can be (CH₂)_rNR₂R_{2a}. Furthermore, motivation and preferences are found as the prior art discloses the compounds of c (page 161, Table 4 and compounds 228-230, page 168) which have a

Art Unit: 1626

phenyl attached to the pyrazole substituted with fluorine and cyano; a trifluoromethyl attached to the pyrazole; a 2-fluoro-phenyl for position A substituted by an imidazole which provides direction and motivation to prepare applicants' instantly claimed compound. Lastly, in regards to the maleic acid salt, the prior art discloses pharmaceutically acceptable salts and exemplifies maleic acid on page 38. Therefore, the rejection of claim 28 as being unpatentable over WO 99/32454 is maintained.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

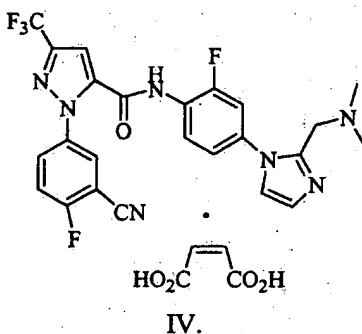
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

Art Unit: 1626

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/32454.

Applicants' instant claim 28 claims a compound of formula IV:



Determining the scope and contents of the prior art

WO 99/32454 discloses compounds, which are inhibitors of factor Xa useful for the treatment of thromboembolic disorders (page 1), of the formula I (page 4) wherein ring M can contain an additional nitrogen atoms, J can be N, D can be CN, E can be phenyl, R can be F, G can be absent, Z can be $(CH_2)_rC(O)NR_3(CH_2)_r$, R1a and R1b can be $-(CH_2)-R1'$, R1' can be $(CF_2)_r(CF_3)$, (pages 5-6), A can be phenyl and B can be a 5-10 membered heterocyclic system substituted with R4a, wherein R4a can be $(CH_2)_rNR_2R_{2a}$ wherein R2 and R2a can be alkyl (page 8). A more preferred embodiment of compounds are found on page 13, for example, formula IIa. Page 18 discloses another even more preferred embodiment, for example, the compound of the

Art Unit: 1626

formula IIa wherein D is $-\text{CN}$, E is phenyl substituted with R which can be F, Z is $\text{C}(\text{O})\text{NH}$, R1a can be $-(\text{CH}_2)_r\text{R1}'$, $\text{R1}'$ can be $(\text{CF}_2)_r\text{CF}_3$, A is phenyl substituted with R4 which can be F, B is Y which can be imidazolyl substituted with 0-2 R4a which can be $(\text{CH}_2)_r\text{NR}_2\text{R2a}$ (page 19). Another further preferred embodiment has the compound of the formula IIa wherein E is phenyl, R can be F, Z is $\text{C}(\text{O})\text{NH}$, R1a can be CF_3 , R1b is H, A is phenyl, B is imidazolyl, R2 and R2a can each be CH_3 and R4a can be $\text{CH}_2\text{NR}_2\text{R2a}$ (page 20-21). Page 38 discloses the pharmaceutically acceptable salts, such as, for example, organic acid salts such as maleic acid.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art reference and claim 28 at issue is that the prior art reference generically encompass positional isomers of applicants instantly claimed maleic acid salt of the product of claim 28 and provide preferences towards applicants instant product of claim 28, but do not specifically disclose a maleic acid salt of the product as instantly claimed.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to someone of ordinary skill in the art at the time of the invention, when faced with WO 99/32454 to prepare the maleic acid salt of the product as instantly claimed in claim 28 as the prior art reference provides compounds which are useful as factor Xa inhibitors and generically encompasses positional isomers of applicants instantly claimed product, provides preferences towards applicants instantly claimed product and provides maleic acid as a pharmaceutically acceptable salt. The motivation to prepare applicants' instantly claimed compound comes from the preferred embodiments of the prior art reference and the expectation of

Art Unit: 1626

preparing additional compounds useful for the treatment of thromboembolic disorders. Furthermore, nothing unobvious is seen in substituting the claimed isomer for the structurally similar isomer, as taught by WO 99/32454 since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. In re Norris, 84 USPQ 458 (1950).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

Art Unit: 1626

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

2/8/06

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER



Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600